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Pesticide Fact Sheet Number 128: Lactofen

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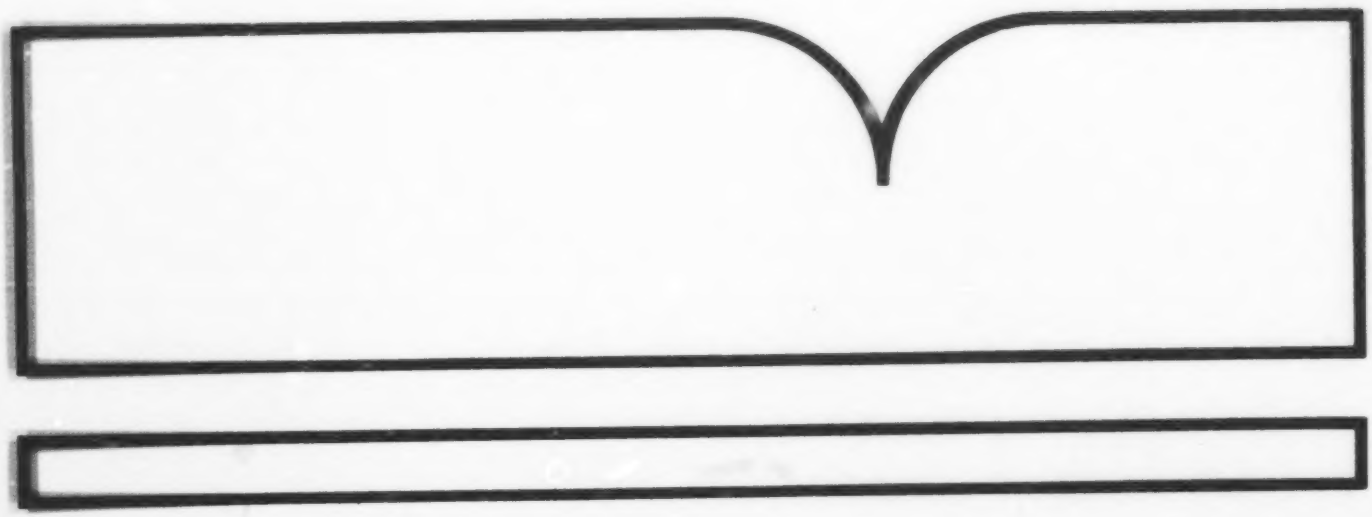

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This document contains up-to-date chemical information, including a summary of the Agency's regulatory position and rationale, on a specific pesticide or group of pesticides. A Fact Sheet is issued after one of the following actions has occurred.

1. Issuance or reissuance of a registration standard,
2. Issuance of each special review document,
3. Registration of a significantly changed use pattern,
4. Registration of a new chemical, or
5. An immediate need for information to resolve controversial issues relating to a specific chemical or use pattern.

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EPA

Pesticide Fact Sheet

Name of Chemical: Lactofen
Reason for Issuance: New Chemical Registration
Date Issued: March 18, 1987
Fact Sheet Number: 128

1. Description of Chemical

Generic Name:	1-(carboethoxy)ethyl-5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoate
Common Name:	Lactofen
Trade Names:	Cobra™, PPG-844
EPA Shaughnessy Code:	128885
Chemical Abstracts Service (CAS) Number:	77501-63-4
Year of Initial Registration:	1987
Pesticide Type:	Herbicide
Chemical Family:	Diphenyl ethers
Producer:	PPG Industries, Inc.

2. Use Patterns and Formulations

Application sites: Used for postemergent control of broadleaf weeds on the terrestrial food crop - soybeans.

Types of formulations: Manufacturing-use product containing 60% active ingredient (ai). End-use product containing 23.2% ai formulated as an emulsifiable concentrate.

Ususal carrier: Water. Crop oil concentrates and surfactants may also be used with the agricultural use formulation.

Types and methods of application: Lactofen is applied by both ground and aerial application.

Application rates: Application rates for soybeans range from 10 to 12.5 fluid ounces per acre (0.16 to 0.2 lb/ai/A) depending on the target weed species.

3. Science Findings

Summary Science Statement: Lactofen has been found to be oncogenic in mice and rats and has been classified as a Group B2 oncogen (Probable Human Carcinogen). A quantitative risk estimate has been conducted for the use of lactofen on soybeans. Based on a $Q^* = 1.7 \times 10^{-1}(mg/kg/day)^{-1}$ and using a Theoretical Maximum Residue Contribution (TMRC) of 0.000017 mg/kg (1.5 kg diet) the "worst case" dietary risk was calculated to be 2.9 incidences in a million (2.9×10^{-6}). Using the TMRC provides a conservative estimate since it does not consider the effect of processing on residue levels in the raw agricultural commodity, that actual residue levels will be lower than the tolerance level (0.05 ppm), and that less than 100 percent of the crop is treated. The 0.05 ppm level is based on a conservative assumption that lactofen and its four metabolites could each be theortically present in an amount just below the level of dectection of the individual compounds (0.01 ppm).

Based on exposure estimates for use of lactofen on soybeans and the Q^*, the following ranges in risk numbers were calculated:

Private Applicators	
Ground boom application:	
Low	10^{-7}
Mean	10^{-6}
High	10^{-4} to 10^{-5}
Mixing, loading, and spraying:	
Open loading system	10^{-5} to 10^{-6}
Closed loading system	10^{-7}
Commerical Applicators	
Aerial application	
Pilots:	10^{-5} to 10^{-6}
Flaggers:	10^{-5}
Mixing/loading/aerial application:	
Open loading system	10^{-3} to 10^{-4}
Closed loading system	10^{-5}
Ground Boom application	
Mixing loading and spraying	
Open loading system	10^{-4}
Closed loading system	10^{-4} to 10^{-5}

These estimates assume that workers are wearing long-sleeved shirts, long pants, and shoes; protective gloves are worn during mixing and loading, and 10 percent dermal absorption.

Lactofen is not considered to be teratogenic and the chemical did not significantly impair reproductive ability in a two-generation reproductive effects study in rats. Four mutagenicity studies with lactofen were negative. A second Ames test was positive.

Lactofen is not acutely toxic to humans or avian species. The pesticide is highly toxic to fish and moderately toxic to aquatic invertebrates. Environmental fate studies show that lactofen does not persist significantly in the environment, that it is relatively immobile, and therefore should not pose a risk of leaching to ground water.

An applicator carcinogenic warning and fish toxicity statements are required to appear on the product's labeling.

Chemical Characteristics:

Physical state: White crystalline solid (Pure Grade Active Ingredient [PGAI])

Molecular formula: C_{19} H_{15} Cl F_3 NO_7

Molecular weight: 461.8

Odor: Very faint aromatic

Solubility: 96 ppb (22 °C) in water
(low solubility)

Melting point: 43.9 - 45.5 °C (PGAI)

Vapor pressure: 8 x 10^{-9} mmHg at 25 °C (extrapolated)
(nonvolatile)

Toxicological characteristics:

Acute oral toxicity (rat): 5960 mg/kg
(relatively nontoxic)

Acute dermal toxicity (rabbit): Greater than 2000 mg/kg
(moderately toxic)

Acute Inhalation: Greater than 6.3 mg/L
(moderately toxic)

Dermal sensitization: Nonsensitizing

Primary Dermal Irritation: Very slight erythema subsiding within 76 hours.

Primary Eye Irritation: Redness of iris and redness and chemosis of the conjunctiva disappearing by 72 hours post-administration.

Subchronic Effects: In a 90-day feeding study in the rat at doses of 40, 200 and 1000 ppm, the no-observed-effect level (NOEL) is 200 ppm (10 mg/kg/day) and lowest-observed-effect level (LOEL) is 1000 ppm (50 mg/kg/day).

Chronic effects:

Chronic Feeding/
Oncogenicity: An 18-month oncogenicity study in CD-1 mice at doses of 10, 50, and 250 ppm in the diet was positive for oncogenic response. A statistically significant increased combined incidence of liver adenomas and carcinomas was observed at 250 ppm in both sexes. The lowest dose, 10 ppm (1.5 mg/kg/day), was the LOEL with increased liver weight and hepatocylomegally.

A 2-year chronic feeding/oncogencity study in Sprague-Dawley rats at doses of 500, 1000, and 2000 ppm in the diet was positive for oncogenic response. A statistically significant increase of liver neoplastic nodules and foci of cellular alteration was observed in both sexes at 2000 ppm. The systemic NOEL is 500 ppm (25 mg/kg/day) and the LOEL is 1000 ppm (50 mg/kg/day) based on kidney and liver pigmentation.

In a 1-year feeding study with beagle dogs, the NOEL is 200 ppm (5 mg/kg/day) and the LOEL is 1000/3000 ppm (25/75 mg/kg/day) based on renal dysfunction, and decreased Hgb, Hct, RBC and cholesterol.

Mutagenicity: Unscheduled DNA synthesis, chromosomal aberration, DNA repair assay, and one Ames Study are negative. A second Ames test in strain TA 1538 of Salmonella typhimurium at 5000 and 7500 ug/plate (precipitates formed in plates) is positive.

Two-Generation Reproduction (rat): Charles River CD rats were dosed with 0, 50, 500, and 2000 ppm lactofen in the diets. The reproductive NOEL is 50 ppm (2.5 mg/kg/day) and the LOEL is 500 ppm (25 mg/kg/day) based on reduced mean pup weight, and increased pup heart and liver weight.

Developmental Toxicity: Sprague-Dawley rats were dosed with 0, 15, 50, and 50 mg/kg/day lactofen in the diet. The maternal and developmental toxicity NOEL is 50 mg/kg and the LOEL is 150 mg/kg/day based on maternal post implantation loss and reduced body weight and fetal bent ribs.

New Zealand White rabbits were dosed with 0, 1, 4, and 20 mg/kg/day lactofen in the diet. The NOEL is 4 mg/kg/day and the LOEL is 20 mg/kg/day based on reduction in maternal food consumption with no developmental toxicity occurring at any dose level tested.

Physiological and Biochemical Behavior Characteristics:

Foliar absorption: Contact activity results in relatively rapid knockdown of weeds.

Translocation: In presence of rainfall, plants absorb lactofen from soil by root uptake.

Environmental Characteristics:

Lactofen is relatively stable to hydrolysis at 25 °C in pH 5 and pH 7 but rapidly hydrolyzes in pH 9 solutions. Lactofen was found to degrade quickly under aerobic soil conditions and degrades under anaerobic conditions. Lactofen half-life under photolysis conditions was 23 days. Lactofen was found to be immobile in soil. Degradation products are highly mobile in sandy soils and have moderate to low mobilities in soils that have a high silt and clay content. However, in an aged column leaching study total radioactivity found in the leachate comprised only 0.27 percent of that applied and was determined to be extensively degraded products. Lactofen was found to have a field dissipation rate of less than or equal to 7 days in a variety of soils. Field rotational crop data indicate residues are not taken up by grains, leafy vegetable, or root crops. Lactofen was found to accumulate in bluegill sunfish with a bioaccumulation factor of 380X for whole fish after 30 days. Depuration was rapid.

Ecological Characterisics:

Avian acute oral toxicity:
Bobwhite quail > 2510 mg/kg
(Practically nontoxic)

Avian dietary toxicity:
Mallard duck and bobwhite quail > 5620 ppm
(Practically nontoxic)

Freshwater fish acute toxicity
Blugill sunfish: > 100 ppb[1/]
0.46 ppm[2/]
(Highly toxic)

Rainbow trout: > 100 ppb[1/]
0.81 ppm[2/]
(Highly toxic)

Freshwater fish 7-day flow-through: > 100 ppb[1/]

Aquatic invertebrate acute toxicity
Daphnia magna: > 100 ppb[1/]
2.0 ppm (TGAI above solubility)
4.8 ppm[2/]
(Moderately toxic)

Honey Bee acute contact toxicity: > 160 ug/bee
(Practically nontoxic)

Fish early life stage toxicity
(Sheepshead minnow): Maximum acceptable toxicant concentration > 0.78 < 1.6 ppm.

These data indicate that lactofen is essentially nontoxic to avian species and bees; and that it is highly toxic to fish and moderately toxic to aquatic invertebrates. Based on the acute and chronic data no significant problems to nontarget organisms are expected from lactofen's use on soybeans.

4. Tolerance Assessment

Tolerances have been established for the combined residues of lactofen and its metabolites containing the diphenyl ether linkage in or on the following raw agricultural commodity (40 CFR 180.):

Commodity	Tolerance (ppm)
Soybeans	0.05

There are no international tolerances/residue limits for lactofen.

1/Maximum solubility of technical grade active ingredient (TGAI)
2/Expressed as active ingredient derived from studies conducted with end-use product.

There are sufficient residue chemistry data available to support this tolerance, including plant and animal metabolism, storage stability (for both the parent compound and its metabolites), field residue studies, and analytical methods. Cattle and poultry feeding studies were not submitted. However, under the proposed conditions of use, measurable residues are not expected to be found in the raw agricultural commodities or fractions. These data are therefore not now necessary.

The Acceptable Daily Intake (ADI) and the Maximum Permissible Intake (MPI) are two ways of expressing the amount of a substance that the Agency believes, on the basis of the results of data from animal studies and the application of "safety" or "uncertainty" factors, may safely be ingested by humans without risk of adverse health effects. The ADI is expressed in terms of milligrams (mg) of the substance per kilogram (kg) of body weight per day (mg/kg/day). The MPI, a related figure, is obtained by assuming a human body weight of 60 kg, and is expressed in terms of mg of substance per day (mg/day).

The Agency has calculated an ADI for lactofen of 0.0015 mg/kg/day, based on a LOEL of 1.5 mg/kg/day in the mouse oncogenicity study and a thousandfold safety factor. The MPI for a 60 kg person is 0.09 mg/day. These tolerances have a theoretical maximum residue contribution (TMRC) of 0.000017 mg/day in a 1.5 kg diet and would utilize 1.13 percent of the ADI.

5. Contact Person At EPA

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